SPECT TRACERS
Ti-201, Tc-99m Sestamibi, Tc-99m Tetrofosmin

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Outline

• Ideal Physiologic Characteristics of MPI radioactive tracers
• Thallium-201
• Tc-99m labelled tracers
  – Sestamibi
  – Tetrofosmin
Clinical Indications for Myocardial Perfusion Imaging

- Evaluation of known or suspected CAD
- Risk stratification
- Preoperative evaluation
- Myocardial viability
- Assessment of acute chest pain in the ER
Ideal Physiologic Characteristics of Radioactive MPI tracers

• Myocardial uptake of the radiotracer
  – proportional to the regional myocardial blood flow over a relatively wide range of blood flows
  – High enough to allow for detection of regional inhomogeneity by external gamma scintigraphy
Ideal Physiologic Characteristics of Radioactive MPI tracers

• Effect of blood flow on myocardial transport of the tracer must be predominant to the effect of metabolic cellular alterations

• Initial myocardial distribution of the radiotracer at the time of injection must remain stable during the acquisition time of the images

• Rapid clearance from the blood.
Blood clearance of radiotracers

- Stop exercise with $^{201}$TI
- Stop exercise with $^{99m}$Tc sestamibi and tetrofosmin
Properties of SPECT Tracers

[Diagram showing cell membrane with extracellular and intracellular compartments, indicating the movement of Na and K ions, and the use of 99mTc sestamibi and 99mTc tetrofosmin.]
Thallium - 201
Thallium-201

- Cyclotron produced monovalent cation with biologic properties similar to potassium
- 60-80 KeV mercury x-ray emission
- 73 hour physical half-life
- Peak myocardial concentration within 5 minutes of IV injection, first pass extraction of 85%
- It cannot be sequestered intracellularly by myocytes if irreversible sarcolemmal membrane injury occurs.
Radioactive Decay Curve

- $T_{1/2} = 73$ hrs
- $T_{1/2} = 6$ hrs

Dose, %

Hours

- $^{99m}Tc$
- $^{201}TI$
Thallium-201

- Redistribution begins 10 to 15 minutes after injection
  - Dependent on:
    - Rate of influx of Tl-201 into the myocardium from whole body blood pool activity
    - Rate of clearance (differential washout) – viable myocardium
    - Blood thallium levels

- Rapid clearance from the intravascular compartment
Thallium-201 Stress-Redistribution

The graph illustrates the time course of $^{201}$TI activity in myocardial uptake and redistribution. The lines represent different conditions:

- **Normal**: Dotted blue line.
- **Ischemic**: Solid red line.
- **Scarred**: Dashed green line.
- **Blood**: Solid purple line.

The x-axis represents time in hours (0 to 3 hours), and the y-axis represents $^{201}$TI activity. The graph shows the post-stress myocardial uptake and the redistribution of $^{201}$TI over time.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sens</th>
<th>Spec</th>
<th>Rate</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahmarian</td>
<td>87%</td>
<td>87%</td>
<td>------</td>
<td>77%</td>
<td>93%</td>
</tr>
<tr>
<td>Tamaki</td>
<td>98%</td>
<td>91%</td>
<td>------</td>
<td>91%</td>
<td>92%</td>
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<tr>
<td>DePasquale</td>
<td>95%</td>
<td>74%</td>
<td>------</td>
<td>79%</td>
<td>89%</td>
</tr>
<tr>
<td>Van Train</td>
<td>94%</td>
<td>44%</td>
<td>82%</td>
<td>77%</td>
<td>65%</td>
</tr>
<tr>
<td>Maddahi</td>
<td>95%</td>
<td>56%</td>
<td>86%</td>
<td>80%</td>
<td>71%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>93%</td>
<td>72%</td>
<td>83%</td>
<td>80%</td>
<td>84%</td>
</tr>
</tbody>
</table>

3 Circulation 1988;77:316-327.
5 JACC 1989;14:1689-1699.
Thallium-201 Stress-Redistribution Protocol

- 2–4 mCi $^{201}\text{TI}$ injection
- Stress injection
- Stress image
- Redistribution image

Time, $h$
Thallium-201 Stress – Late Redistribution Protocol

Thallium Rest-Redistribution Protocol

2.5–4.5 mCi $^{201}$TI injection

- Rest image
- Redistribution image

Time, $h$

- 0 (30 min)
- 1
- 2
- 3
- 4
- 5
Prognostic value of tomographic rest-redistribution thallium 201 imaging in medically treated patients with coronary artery disease and left ventricular dysfunction

Giuseppe Gioia, MD, Elisa Milan, MD, Raffaele Giubbini, MD, Nicholas DePace, MD, FACC, Jaekyeong Heo, MD, FACC, and Abdulmassih S. Iskandrian, MD, FACC

89 patients

• Inclusion Criteria
  – Documented CAD (>50% diameter stenosis on ≥ 1 coronary artery based on CAG)
  – LV ejection fraction <50%

• Exclusion Criteria
  – Recent AMI
  – Undocumented CAD
## Comparison of Clinical and Imaging Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Alive (n=48)</th>
<th>Dead (n=33)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Men/Women</td>
<td>38/10</td>
<td>21/12</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67±12</td>
<td>71±11</td>
<td>0.08</td>
</tr>
<tr>
<td>LVEF</td>
<td>27±7</td>
<td>26±8</td>
<td>NS</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td>2.3 ±0.8</td>
<td>2.5 ±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>No. of abnormal segments</td>
<td>13± 5</td>
<td>12 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>No. of reversible segments</strong></td>
<td><strong>2±4</strong></td>
<td><strong>4±5</strong></td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>No. of segments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild fixed defects</td>
<td>4±4</td>
<td>4±4</td>
<td>NS</td>
</tr>
<tr>
<td>Severe fixed defects</td>
<td>6±5</td>
<td>5±5</td>
<td>NS</td>
</tr>
<tr>
<td>Thallium redistribution (n/%)</td>
<td>18/38</td>
<td>22/67</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Journ of Nuc Cardio, 1996;3:150-156.*
Actuarial Survival Curve

Mantel-Cox = 5
p = 0.03

Prognostic Value of Rest-Redistribution Tomographic Thallium-201 Imaging in Ischemic Cardiomyopathy

Giuseppe Gioia, MD, Joseph Powers, MD, Jaekyeong Heo, MD, and Abdulmassih S. Iskandrian, MD, with the technical assistance of Joseph Russell, CNMT, and David Cassel, BS

Am Journ of Cardio 1995;75:759-762
85 patients

• Inclusion Criteria
  – Documented CAD (>50% diameter stenosis on ≥ 1 coronary artery based on CAG)
  – LV ejection fraction <50%

• Exclusion Criteria
  – Recent AMI
  – Unstable Angina pectoris

Am Journ of Cardio 1995;75:759-762
## Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Coronary Revascularization (n=38)</th>
<th>Medical Therapy (n=47)</th>
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<tr>
<td><strong>Men (%)</strong></td>
<td>30 (79)</td>
<td>34 (72)</td>
</tr>
<tr>
<td><strong>Q wave MI (%)</strong></td>
<td>23 (61)</td>
<td>30 (64)</td>
</tr>
<tr>
<td><strong>Angina Pectoris (%)</strong></td>
<td>26 (68)</td>
<td>26 (55)</td>
</tr>
<tr>
<td><strong>CHF (%)</strong></td>
<td>13 (34)</td>
<td>16 (34)</td>
</tr>
<tr>
<td><strong>Systemic HPN (%)</strong></td>
<td>15 (39)</td>
<td>18 (38)</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus (%)</strong></td>
<td>13 (34)</td>
<td>16 (34)</td>
</tr>
</tbody>
</table>

*Am Journ of Cardio 1995;75:759-762*
Distribution of perfusion defects

Am Journ of Cardio 1995;75:759-762
**Actuarial Life Table Analysis**

Annual Mortality Rate
6% surgical vs 13% medical group

*Mantel-Cox = 3*

*P = 0.056*

*Am Journ of Cardio 1995;75:759-762*
Improved Outcome after CABG in Ischemic Cardiomyopathy and Residual Myocardial Viability

*70 patients with multivessel CAD and LVEF <40%
Rest-redistribution TI-201 protocol
Viability index = sum of viability scores / no. of segments

Pagley PR, et. al.
Circulation 1997;96:793-800.
Blood Activity of Thallium in relation to uptake and clearance

Dilsizian V, Rocco TP, et. al.
Thallium reinjection

Dilsizian V, et. al.
NEJM 1990; 323:141-146.
Thallium reinjection

Dilsizian V, et. al.  
NEJM 1990; 323:141-146.
Incremental prognostic value of Ti-201 reinjection

* Prior MI and LV dysfunction

Petretta m, et. al.
Increase Lung Uptake with TI-201
$^{99m}\text{Tc}$-hexakis-methoxyisobutylisonitrile
(Tc-99m Sestamibi)
Tc-99m-Sestamibi

- Lipid soluble cationic compound produced from a molybdenum generator
- 140 keV photopeak energy
- 6 hour physical half-life
- First pass extraction 60%
- Slow clearance from the intravascular compartment via hepatobiliary excretion
- Minimal redistribution when compared to Tl-201 (image ACS patients)
Tc-99m-Sestamibi

• Accumulation and clearance kinetics were dependent on sarcolemmal integrity and on aerobic metabolism.

• Greatest concentration is found in the gallbladder and liver. (immediately and 60 minutes after injection)

• 5 to 10% of patients experienced a transient metallic or bitter taste (copper salt)
Advantages of MIBI over Thallium 201

• Better radiation dosimetry allows injection of a higher dose resulting to a better image resolution and quality

• Gated acquisition for assessing regional wall motion and thickening
**Tc-99m-MIBI or TETRO**

**Two Day Protocol**

Tc-99m MIBI/TETRO 15-25 mCi

STRESS

15 mins

Stress Image

24 hours

Tc-99m MIBI/TETRO 15-25 mCi

Rest Image

30 mins - 1 hr

STRESS
Tc-99m-MIBI or TETRO
Same Day Rest-Stress Protocol

Tc-99m MIBI/TETRO
10 mCi

Rest Image
30 mins-1 hr

STRESS
3 hrs

Stress Image
15 mins
$^{99m}$Tc-MIBI and $^{201}$TI activities in canine myocardial biopsies

Li QS, Solot G, et. al.
Jour Nuc Med 1990;31:1069-1076
## Sensitivity & Specificity of TI-201 and MIBI SPECT imaging for CAD

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Normalcy</th>
<th>Individual Vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sens</td>
<td>Spec</td>
<td>Rate</td>
</tr>
<tr>
<td></td>
<td>Tc-MIBI</td>
<td>TI-201</td>
<td>Tc-MIBI</td>
</tr>
<tr>
<td>Kiat et al (^1)</td>
<td>93%</td>
<td>80%</td>
<td>75%</td>
</tr>
<tr>
<td>Kahn et al (^2)</td>
<td>95%</td>
<td>84%</td>
<td>--</td>
</tr>
<tr>
<td>Iskandrian (^3)</td>
<td>82%</td>
<td>82%</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>90%</td>
<td>83%</td>
<td>93%</td>
</tr>
</tbody>
</table>

\(^1\) Am Heart Journ 1989;117:1-11  
\(^2\) Circulation 1989;79:1282-1293  
\(^3\) Am Heart Journ 1989;64:270-275
Comparison of Ti-201 and MIBI uptake in chronic stable CAD patients with LV dysfunction

OPEN - Initial Rest Ti-201 uptake

HATCHED - Redistribution Ti-201 uptake

SOLID - Rest MIBI uptake

* Mild <75% but >50% uptake

* 20 patients with stable CAD and LVEF <35%

Comparison of TI-201 and MIBI uptake in chronic stable CAD patients with LV dysfunction

OPEN - Initial Rest TI-201 uptake

HATCHED - Redistribution TI-201 uptake

SOLID - Rest MIBI uptake

* Severe = <50% uptake

* 20 patients with stable CAD and LVEF <35%

Comparison of resting uptake with TI-201 and MIBI

Udelson JE, et. al.
Circulation 1994;89:2552-2561
Comparison of TI-201 and MIBI for estimating the extent of mass defect

STRESS IMAGES

* 24 patients with prior MI underwent exercise for an identical duration and external work load during stress

Narahara et. al.  
Cellular Kinetics of Tl-201 and MIBI

*Oxidative phosphorylation inhibited by rotenone
Glycolysis inhibited by iodoacetate

Piwnica – Worms D, et. al.
Prognostic Implications of Tc-99m Sestamibi Viability Imaging and Subsequent Therapeutic Strategy in Patients With Chronic Coronary Artery Disease and Left Ventricular Dysfunction

Roberto Sciagrà, MD, Marco Pellegrini, MD, Alberto Pupi, MD, Leonardo Bolognese, MD,* Gianni Bisi, MD,† Vito Carnovale, MD, Giovanni M. Santoro, MD*
105 patients underwent MIBI rest – nitrate SPECT

- Documented CAD by CAG
- Reduced global LV function (EF <50% by echocardiography or radionuclide ventriculography)
- Severely abnormal regional wall motion in at least one coronary artery territory

• Excluded
  - Unstable angina
  - Recent MI (<2 months)

JACC 2000;36:739-745.
• Wall motion of each segment was scored from 1 (normokinesia) to 4 (dyskinesia)
  – Segments with score ≥2 were considered asynergic

• Asynergic segments were defined viable if an activity increase >10% in nitrate SPECT compared to baseline imaging.

• Viability was considered to be present if activity in nitrate SPECT was ≥65%.
• Patient treatment
  – Group 1 = medical therapy
  – Group 2 = coronary revascularization
    • 2A = complete
    • 2B = incomplete

• Mean follow-up 27 ± 22 months.
<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 26)</th>
<th>Group 2A (n = 55)</th>
<th>Group 2B (n = 24)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63.7 ± 10.1</td>
<td>59.6 ± 10.3</td>
<td>59.5 ± 11.4</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>96%</td>
<td>87%</td>
<td>88%</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>85%</td>
<td>87%</td>
<td>83%</td>
<td>NS</td>
</tr>
<tr>
<td>Angina</td>
<td>38%</td>
<td>51%</td>
<td>42%</td>
<td>NS</td>
</tr>
<tr>
<td>CCS classification</td>
<td>1.3 ± 0.4 [1]</td>
<td>1.2 ± 0.5 [1]</td>
<td>1.3 ± 0.4 [1]</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>1.8 ± 0.7 [2]</td>
<td>1.4 ± 0.5 [1]</td>
<td>1.5 ± 0.6 [1]</td>
<td>Gr. 1 vs. 2a &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gr. 1 vs. 2 &lt; 0.05</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>31.5 ± 10.2</td>
<td>35 ± 9</td>
<td>34 ± 8.4</td>
<td>NS</td>
</tr>
<tr>
<td>Diseased vessels</td>
<td>2 ± 0.7 [2]</td>
<td>2.1 ± 0.9 [2]</td>
<td>2.5 ± 0.5 [3]</td>
<td>Gr. 1 vs. 2b &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gr. 2a vs. 2b &lt; 0.05</td>
</tr>
<tr>
<td>Coronary artery jeopardy score</td>
<td>5.5 ± 2.5 [6]</td>
<td>6.5 ± 2.9 [6]</td>
<td>7 ± 2.1 [7]</td>
<td>Gr. 1 vs. 2b &lt; 0.05</td>
</tr>
<tr>
<td>Viable asynergic segments</td>
<td>4.8 ± 2.4 [5.5]</td>
<td>4.5 ± 2.6 [4]</td>
<td>4.7 ± 2.9 [4]</td>
<td>NS</td>
</tr>
<tr>
<td>CABG/PTCA</td>
<td>NA</td>
<td>35/20</td>
<td>7/17</td>
<td>&lt; 0.05</td>
</tr>
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</table>
Survival Curves of Treatment Groups

Comparison of survival rates for different groups over the follow-up period. Group 1 (n = 26), Group 2A (n = 55), Group 2B (n = 24).

Log Rank Test:
- Group 1 vs. 2A: 3.6, p < 0.0002
- Group 1 vs. 2B: 1.2, p = 0.11
- Group 2A vs. 2B: 1.9, p < 0.03

JACC 2000;36:739-745.
Survival Curve according to number of Non-revascularized Viable Asynergic Segments

Log Rank Test
None vs. 1-3: 1.36, p = 0.08
None vs. >3: 3.86, p < 0.0001
1-3 vs. >3: 1.63, p = 0.05

JACC 2000;36:739-745.
1,2-{bis(bis(2-ethoxyethyl)phosphino)ethane (Tc-99m-Tetrofosmin)
Tc-99m-Tetrofosmin

- Lipid soluble cationic compounds
- Similar myocardial uptake, retention and blood clearance kinetics to MIBI
- Images can be obtained as early as 5 minutes after injection
- First pass extraction is 54%.
- Faster clearance from both the liver & lungs compared to that of MIBI
- Myocardial uptake and retention is dependent on mitochondrial membrane potential
# Accuracy of Tc-99m Tetrofosmin SPECT in the evaluation of CAD

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>LAD</th>
<th>LCX</th>
<th>RCA</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>95%</td>
<td>71%</td>
<td>61%</td>
<td>73%</td>
</tr>
<tr>
<td>Specificity</td>
<td>77%</td>
<td>94%</td>
<td>96%</td>
<td>91%</td>
</tr>
<tr>
<td>Normalcy Rate</td>
<td>93%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*235 patient suspected or known CAD
61 patients with low likelihood of CAD

Azzarelli S, et. al.
Quantitative regional tracer uptake between rest-redistribution Tl-201 and Rest Tc-99m Tetrofosmin imaging

Galassi A, et. al.
Journ of Nuc Cardio 1998;5:56-63
SUMMARY

• All SPECT radiotracers exhibit a “roll off” phenomenon at high coronary blood flow levels which may underestimate regional myocardial blood flow especially those with mild CAD.
SUMMARY

• *Thallium*
  – Has a long physical half-life
  – High extraction fraction compared to MIBI or tetrofosmin
  – Redistribution has prognostic value in viability determination
  – Reinjection of 1 mCi of thallium at rest immediately after 3-4 hour redistribution-stress redistribution studies improves the assessment of myocardial ischemia and viability.
SUMMARY

• *Tc-99m agents*
  – Has a high photopeak energy which is optimal for imaging with improved resolution due to less Compton scatter
  – Slow myocardial clearance with no redistribution
  – Adding nitrate enhances detection of viable myocardium